The Total Synthesis of (±)-Chamigrene

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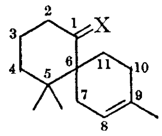
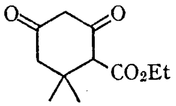
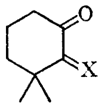
DURING studies on the synthesis of terpenoids, we have prepared 5,5,9-trimethylspiro[5,5]undec-8-en-1-one (I), which corresponds to a convenient precursor for the synthesis of chamigrene (II), a new sesquiterpene hydrocarbon, very recently isolated from the leaf oil of *Chamaecyparis taiwanensis*.[1] We describe here the synthesis of (I) and its transformation to (±)-chamigrene (II).



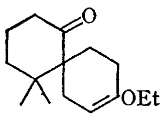
(I) X = O
(II) X = CH$_2$
(Chamigrene)



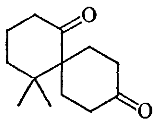
(III)



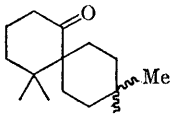
(IV) X = H, CH$_2$OH
(V) X = CH$_2$



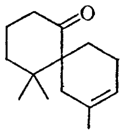
(VI)



(VII)



(VIII)



(IX)

The known *cisoid* αβ-unsaturated ketone (V)[2] was chosen as the key intermediate and prepared from 4-ethoxycarbonyl-5,5-dimethylcyclohexane-1,3-dione (III)[3] according to the reported reaction sequences.[2,3] A decalin solution of the intermediate (V), obtained by co-distillation with decalin during dehydration of the hydroxymethyl ketone (IV) with toluene-*p*-sulphonic acid as described in the literature,[2] was immediately* treated with an excess of 2-ethoxybuta-1,3-diene† at 200° for 5 hr. in an autoclave to give 20% of a single crystalline adduct, 9-ethoxy-5,5-dimethylspiro[5,5]undec-8-en-1-one (VI), m.p. 75—76°, i.r. (CCl$_4$) 1707 and 1675 cm.$^{-1}$, n.m.r. (CCl$_4$) 0·82 and 0·93 (*gem*-Me$_2$), 1·19 (triplet) and 3·59 (quartet) (OEt), 4·38 p.p.m. (multiplet, =CH). The location of the ethoxy-group at C-9 would be most probable from the known generality of the direction in the Diels–Alder addition between 2-ethoxybuta-1,3-diene and αβ-unsaturated carbonyl compounds.[6] Hydrolysis of (VI) with dilute alcoholic hydrochloric acid gave an oily diketone (VII) in 94% yield, i.r. (CCl$_4$) 1716 and 1704 cm.$^{-1}$, mono-2,4-dinitrophenylhydrazone (a C=O absorption at 1697 cm.$^{-1}$ remains), m.p. 134·5—135·5°, which was then treated with two molecular equivalents of methylmagnesium iodide in ether at room temperature for 2 hr. to yield 75% of a mixture of epimeric keto-alcohols (VIII).‡ Dehydration of (VIII) with thionyl chloride–pyridine produced 5,5,9-trimethylspiro[5,5]undec-8-en-1-one (I) in 50% yield, m.p. 70·5—71·5°, i.r. (CCl$_4$) 1706 and 1667 cm.$^{-1}$, n.m.r. (CCl$_4$) 0·80 and 0·93 (*gem*-Me$_2$), 1·58 (=C·Me) and 5·26 p.p.m. (multiplet, =CH). In practice for the preparation

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* It has been reported that the compound (V) readily undergoes dimerisation (ref. 2). For the structure of the dimer of 2-methylenecyclohexanone, see ref. 4.

† 2-Ethoxybuta-1,3-diene was prepared from methyl vinyl ketone according to the procedure of ref. 5.

‡ One of the epimers was rapidly eluted from a column of neutral alumina in pure form. It had m.p. 113—113·5° and absorptions at 3270 and 1702 cm.$^{-1}$ in the i.r. (Nujol), and at 0·91 (*gem*-Me$_2$) and 1·11 p.p.m. (–O–C–Me) (CCl$_4$; 60 Mc.).

of (I) it was more convenient to conduct the Diels–Alder reaction on (V) using isoprene under identical conditions. Thus, the compound (I) was obtained in *ca.* 20% yield accompanied by an oily isomer (*ca.* 12% yield), being presumably the 8-methyl isomer (IX); these were separated by crystallisation from petroleum (or methanol) after seeding with a pure sample of (I).

Reaction of the unsaturated ketone (I) with an excess of methylenetriphenylphosphorane–dimethyl sulphoxide[7] at 55—60° for 48 hr. gave the hydrocarbon (II), in 70% yield, identical with a sample of natural chamigrene on vapour-phase or thin-layer chromatography and spectroscopically (i.r., n.m.r.).§ The authors are grateful to Professor S. Itô for providing a sample of natural chamigrene and the spectral data prior to publication. They also acknowledge support from the Ministry of Education of Japan and the Matsunaga Foundation.

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§ Satisfactory analytical data were obtained for all the new compounds. Chemical shifts are in p.p.m. downfield from Me_4Si.

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